Journal of Chemical Biology & Therapeutics

Dey et al., J Chem Biol Ther 2016 1:2
DOI: 10.4172/2572-0406.1000107

Review Article Open Access

Anti-inflammatory and Anti-tumor Activities of Parthenolide: An Update

Sananda Dey, Mrinmoy Sarkar and Biplab Giri*

Experimental Medicine and Stem Cell Research Laboratory, Department of Physiology, West Bengal State University, Barasat, Kolkata 700126, India

Abstract

Parthenolide (PTL), the secondary metabolite of feverfew plant (*Tanaceum parthenium*), has been used in various medical purposes globally. Inflammation represents a physiological response to injury and helps to restore tissue homeostasis. Inflammation and cancer both are associated with genotoxicity, invasion, metastasis, and abnormal tissue repair mechanisms. PTL inhibit major cellular inflammatory and proliferation pathways like NFκB, STAT3, and MAPK along with the activity and expression of several inflammatory mediators including COX. *NFκB* pathway plays a key role in controlling cell cycle progression and apoptosis together with metastasis and cancer of various types. Elevated NFκB, Wnt/β-catenin pathways are crucial factors of tumorogenesis. PTL inhibits NFκB and Wnt/β-catenin pathways, and thereby promotes apoptosis and suppresses cell proliferation. Experimental data showed that PTL protects normal cells from apoptosis; whereas in cancer cells it induces apoptotic cell death. Hence, parthenolide could be useful in controlling inflammatory diseases alone or together with tumorogenesis due to its evident anticancer potency and anti-inflammatory nature.

Keywords: Parthenolide; Feverfew; Inflammation; Cancer; Tumor; NFκB

Abbreviations: AML: Acute Myelogenous Leukemia; ARE: Antioxidant Response Element; COX: Cyclo-Oxygenase; FRA-1: Fos Related Antigen-1; HO-1: Heme Oxygenase-1; HDAC1: Histone Deacetylase 1; iNOS: Inducible Nitric Oxide Synthase ; IL1: Interleukin-1; IKK: IκB kinase; IKC: IkB Kinase Complex; JNK: Jun Amino-Terminal Kinases; LT: Leukotrienes; LPS: Lipopolysachharide; MAPK: Mitogen-Activated Protein Kinases; Nrf2: Nuclear Factor (Erythroid-derived 2)-like 2; NFκB: Nuclear Factor Kappa B; PTL: Parthenolide; PGE2: Prostaglandin E2; PKC-a: Protein Kinase C-α; ROS: Reactive Oxygen Species; GSH: Reduced Glutathione; SRF: Serum Response Factor; STAT: Signal Transducers and Activators of Transcription; TCR: T-cell Receptor ; TrxR: Thioredoxin Reductase; TRAF: TNF Receptor Associated Factor; TNFα: Tumor Necrosis Factor Alpha; TYK: Tyrosine Kinases; VEGF: Vascular Endothelial Growth Factor; XBP1: X-box Binding Protein-1

Introduction

Parthenolide (PTL) is a multifunctional naturally occurring compound, isolated from Mexican Indian asteraceae family plants and has been widely used in native folk medical practices, including treatment of inflammation [1], stomach ache, tooth ache, menstrual irregularities, fever, rheumatoid arthritis [2] and migraines [3,4] due to its anti-inflammatory properties [5]. Sesquiterpene lactones are secondary metabolites found in asteraceae family plants. PTL is the principal component of sesquiterpene lactones present in medical plants such as feverfew (*Tanacetum parthenium*) [6]. PTL contains an α-methylene-γ-lactone ring and an epoxide, both of which are able to interact readily with nucleophilic sites of biological molecules [7]. These functional groups can react with nucleophiles, especially with cysteine thiol groups in a Michael addition reaction. Being the primary bioactive component of feverfew, PTL is used as prophylactic treatment for migraine having positive therapeutic effects in clinical trials [8]. PTL has anti-leishmaniasis properties too [9]. Pareek et al. reported that feverfew has been used for psoriasis, allergies, asthma, tinnitus, dizziness and vomiting [10]. PTL has also been reported to improve endotoxic shock and prevent inflammation in immune glomerulonephritis [11,12]. In *in vitro* experiments scientists have shown the nuclear factor kappa B (NFκB) inhibiting abilities of PTL [13]. Zhang et al. showed that PTL inhibits the activation of NFκB and ERK signaling pathways, as well as the expression of inflammatory and osteo-clastogenic genes in lipo-polysaccharide (LPS)-stimulated hPDLCs *in vitro* [14]. It also inhibits proliferation and eliminates various cancer cells predominantly by inducing apoptosis [15]. It was recently reported that PTL inhibits the *in vitro* growth of tumor cells in a cytostatic manner [16]. *In vitro*, it preferentially inhibits mamosphere growth. The decrease of sphere growth was due to the inhibition of NFκB activity [17]. PTL and its derivatives may be effective anticancer agents against cholangiocarcinoma for the reason that they can effectively induce apoptosis in cholangiocarcinoma cells [18,19]. PTL-induced apoptosis was enhanced by the PKC-α inhibitor Ro317549 (Ro) through inhibition of Nrf2 expression and its nuclear translocation, resulting in suppression of HO-1 expression. Both in combination, PTL and Ro efficiently enhanced cancer cell growth inhibition compared to treatment with either agent alone in an *in vivo* tumor xenograft model [19]. Carlisi et al. established that both PTL and its soluble analog dimethylaminoparthenolide (DMAPT) arrested the cell growth of triple negative breast cancer stem cells by suppressing Nrf2, SOD and catalase, and inducing ROS generation and mitochondrial dysfunction, which ultimately leading to apoptotic and necrotic cell death [20]. It has also been observed that pre-incubated HCT116 cells with PTL resulted in the absence of activation of NFκB after TNFα treatment in both p53-proficient and p53-deficient cells [21]. Therefore, parthenolide might be represented a new class of cancer chemotherapeutic agent. This review aims to summarize the medicinal and clinical usages of PTL and its effects on relevant cellular signaling molecules to control inflammatory and tumorogenic pathophysiology.

Anti-inflammatory activity of parthenolide

The sesquiterpene lactone PTL from the anti-inflammatory medicinal herb Feverfew (*Tanacetum parthenium*) could be effective

***Corresponding author:** Biplab Giri, Experimental Medicine and Stem Cell Research Laboratory, Department of Physiology, West Bengal State University, Barasat, Kolkata 700126, India, Tel: 91-9432904884; E-mail: bgiri.emscrl@gmail.com

Received May 30, 2016; **Accepted** June 18, 2016; **Published** June 25, 2016

Citation: Dey S, Sarkar M, Giri B (2016) Anti-inflammatory and Anti-tumor Activities of Parthenolide: An Update. J Chem Biol Ther 1: 107. doi: 10.4172/2572-0406.1000107

against variety of inflammatory responses. The anti-inflammatory properties of PTL, like platelet aggregation [22] and carrageenan-induced mouse and rat paw edema [23], have been summed up by investigations of various scientists. Feverfew appears to be an inhibitor of prostaglandin synthesis [24], leukotrienes (LT) and expression of pro-inflammatory cytokines [25]. PTL inhibited histamine release from rat peritoneal mast cells [26]. Further studies revealed that it inhibits inflammatory mediators including activity and expression of cyclo-oxygenase (COX) specifically COX-2, which also enhances cancer stem-like cells' characteristics such as higher colony formation efficiency and over expression of stemness-associated genes [27-29]. The compound was found to inhibit activation of transcription factor NFκB by both at the transcriptional level and by direct inhibition of associated kinases (IKK-β) [30,31]. NFκB transcription factors regulate several important physiological processes, like immune and inflammatory responses, cell growth and apoptosis. In normal unstimulated cell, NFκB dimers are located in the cytoplasm associated with IκB inhibitor proteins in inactive form. In response to pro-inflammatory molecules like TNF-α, cytotoxic drugs, ionizing radiations and oxidative stress, IκB gets phosphorylated rapidly and finally degraded through ubiquitination and proteasomal degradation [32-34]. The free NFκB dimer translocates to the nucleus and modulates expression of specific genes. Recent research showed that PTL could down regulate NFκB through one of the following ways either inhibiting IκB kinase complex (IKC) or binding with the catalytic subunit of IKK complex i.e., IKK-β subunit as a consequence of inactivation of NFκB signaling pathway [35]. Cellular inflammatory processes are associated with the release of cell-derived intermediaries, including cytokines of the IL-1 and IL-6 families, from the site of inflammation. Sobota et al. showed that parthenolide is also an effective inhibitor of these inflammatory cytokines IL-1 and IL-6. It hinders IL-6 induced gene expression by blocking STAT3 phosphorylation on Tyr705 [36]. PTL inhibits LPS-induced COX-2 protein, mRNA expressions in alveolar macrophage cells, production of IL-1β and prostaglandin E2 (PGE2) and activation of the Akt/mTOR [37,38]. Fiebich et al. investigated the effect of parthenolide on iNOS synthesis and NO release using primary rat microglia and evaluated parthenolide to be an effective inhibitor of iNOS/NO synthesis. PTL induced inhibition of NO synthesis has been implicated to be an effective treatment of certain inflammatory and autoimmune diseases including migraine and multiple sclerosis where NO plays an important role in the etiopathology of the disease (Table 1) [39].

Anticancer/anti-tumorogenic activity of parthenolide

Drug discovery against cancer is ventured throughout the world, especially from the natural harvests. Recently, the anti-tumor property of parthenolide has attracted great interest among researchers. Parthenolide has been shown to inhibit growth or induce apoptosis in a number of tumor cell lines [16-18,40,41]. Many mechanisms have been proposed as being involved in the anti-tumorogenic effect of parthenolide, including inhibition of NFκB activation [17,41], suppression of STAT3 [36], inhibition of MAPK activity [37], sustained activation of JNK [42,43], activation of p53 [15,17], inhibition of nucleic acid synthesis [44,45], depletion of thiols, induction of oxidative stress [16,17], induction of mitochondrial dysfunction [16], disruption of intracellular calcium equilibrium, induction of cell cycle G2/M phase arrest [16,40], depletion of HDAC1 [43], and inhibition of tubulin carboxypeptidase activity [46,47]. Parthenolide also inhibits IL1 and TNFα-mediated NFκB activation [7] resulting in inhibition of IκB kinase mediated NFκB translocation [48]. PTL also induces apoptosis and autophagy-mediated growth inhibition in HeLa cells by repressing the PI3K/Akt signaling pathway and mitochondrial membrane depolarization, bringing on mitochondria-mediated apoptosis, ROS generation and autophagy by activation of caspase-3, up regulation of Bax, Beclin-1, ATG5, ATG3 and down-regulation of Bcl-2 and mTOR [49].

Parthenolide and NFκB

The molecular mechanism of PTL action has been showed associated with inhibiting NFκB mediated apoptosis that enables disruption in recruitment of IKK to the TNF receptor, resulting in blockade of IKK-dependent activation of NFκB, along with activation of the p53 pro-apoptotic pathway, and augmentation of reactive oxygen species (ROS) in cancer cells [43]. In addition to acute myeloid leukemia, PTL targets mammary breast cancer stem cells and could inhibit mamosphere growth for more than seventy two hours. The shrinkage in sphere growth is due to the inhibition of NFκB activity [17]. PTL and its derivatives may be effective anticancer agents against cholangio-carcinoma as it effectively induces apoptosis in these cells [18]. It has also been observed that pre-incubated HCT116 cells with parthenolide resulted in the absence of activation of NFκB after TNFα-treatment in both p53-proficient and p53-deficient cells [21]. PTL could antagonize Taxol-mediated NFκB nuclear translocation as well as activation and Bcl-xl up-regulation by selectively targeting IκB kinase activity. In A549 lung carcinoma cells, inhibition of NFκB by PTL resulted in activation of caspase 9 and 3 by the mitochondrial death pathway involving cytochrome-c release. Moreover, taxol-induced inhibition of A549 cell growth in mouse xenograft was potentiated with the treatment PTL [50]. Another study in mouse xenograft model also showed PTL inhibiting tumor initiation and progression by $CD44^+$ tumor initiating cells. It was found in one of the early events of PTL cytotoxicity that it is associated with attenuation of activity of the non-receptor tyrosine kinase, src and many src-associated signaling components that include: Csk, FAK, β1-arrestin, FGFR2, PI3K, PKC, MEK/MAPK, CaMK, the transcription factor ELK-1 and ELK-1 dependent genes. Additionally, it was observed that PTL altered binding of a number of transcription factors involved in prostate cancer including: C/EBP-α, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT1/3, XBP1 and p53 [51]. Kim et al. showed that PTL inhibits IκBα phosphorylation and NFκB activation, resulting in the initiation of apoptosis and the ultimate repression of colitis-associated colon cancer development *in vivo* [52]. And, in *in vitro* experiments, using human multiple myeloma cells, Kong et al. (2015) showed that PTL treatment resulted in reduced level of p65 and ubiquitination of TNF receptor-associated factor 6 (TRAF6) [53]. It was also observed that PTL suppresses proliferation, invasion and tumor induced angiogenesis of glioblastoma cells. It reduces Akt phosphorylation and mitochondrial apoptotic signaling in addition to its inhibitory action on NF-κB (Table 1) [54].

Parthenolide and STAT

It is previously discussed that the activation of STAT directs to cell proliferation, cell migration, transformation, apoptosis, cellular differentiation, adhesion, fetal development, inflammation, and immune response. In normal homeostasis, STAT tyrosine phosphorylation is short-term, lasting from 30 minutes to several hours, whereas in numerous cancer cell lines and primary tumors it is in NFκB contrary to that of normal homeostasis. It takes place due to the deregulation of positive effectors of STATs activation, such as upstream tyrosine kinases (JAK, TYK), or repression of negative regulators of STATs phosphorylation, e.g. phosphatases, suppressors of cytokine signaling or protein inhibitors of activated STATs [55,56]. The products of STATs-regulated gene transcription, including Bcl-xL and survivin permit cancer cells to proliferate and to inhibit cellular apoptosis episode [57]. In normal cells, survivin is expressed in low

Table 1: Effect of parthenolide on signaling molecules involving inflammatory, cellular proliferation and tumorigenic pathways.

Inflammatory Molecules	References	Cell Proliferation/ Apoptosis associated Molecules	References
NFκB	[14], [30], [31], [35], [43], [48], [90]	NFκB	[17], [18], [21], [52], [54], [64], [78-79], [90]
IKK-β	[30-32], [48]	[ERK/MEK/MAPK/ELK1]	[14], [37], [48], [51]
iNOS	[39]	β1-arrestin, Csk, FAK, FGFR2, PKC	[51]
STAT1/STAT3	[36], [51], [83-88]	STAT1/STAT3	[36], [51], [55-56], [83-88]
Cyclooxygenase (COX)	[27-29], [37]	JNK	[42], [43], [62], [64]
Interleukin-1/6	[7], [36]	Bcl-2 Bcl-2 like-1	[49] [85], [86], [89]
Prostaglandin	[24]	Bcl-xl	[57]
Leukotriene	[25]	TNF-α TNF-α associated factor	[63] [53]
Histamin	[26]	Survivin	[57], [58]
GSH	[16], [14], [43]	GSH	[68]
Nrf2-ARE	[20], [43], [71]	Caspases	[50], [49]
Thioredoxin reductase1& 2	[70]	Bax, Beclin, ATG5, ATG3	[49]
		P53	[51]
		C/EBPα, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT3, XBP1	[51]
		PKC-α, HO-1	[19]

levels whereas in cancer cells it is high and acts as an upstream signal on G2/M transition and cellular proliferation [58]. Survivin has been considered to be a key resistant factor in glioblastoma [59] and leukemia [59] because of its anti-apoptotic action, autophagy regulation, and G_2/M cell cycle promoting effects. It was observed that, treatment with PTL led to substantial down regulation of survivin, G_2/M cell cycle arrest and Chk2 upregulation in glioblastoma cells *in vitro* [61]. According to Sobota et al. PTL blocks STAT-3 and STAT-1 binding to the regulatory elements in DNA. Moreover PTL inhibits phosphorylation of tyrosine 705 residue which prevents translocation to the nucleus and subsequent gene activation by blocking STAT-3 dimerization (Table 1) [36].

Parthenolide and JNK/MAPK

JNK is one of the MAPK groups of protein which are responsive to stress stimuli such as cytokines, UV irradiation, heat shock etc., together with ERKs, p38 and ERK5. All MAPKs are activated by dual phosphorylation of threonine and tyrosine motifs within the sub-domain VIII of activation loop. Once activated, they translocate to the nucleus and phosphorylate target transcription factors, such as c-Jun. JNK involved in apoptosis, neurodegeneration, cell differentiation, proliferation and inflammatory conditions [61]. Won et al. showed that PTL inhibited JNK activation and led to UVB-induced apoptosis of JB6 murine epidermal cells [62]. But Zhang et al. demonstrated that inhibition of NF-κB activation and sustained JNK activation contribute to the sensitization of PTL effect on TNFα- induced apoptosis in human cancer cells [43]. The authors reported that PTL sensitizes human nasopharyngeal carcinoma (CNE1) cells to TNF-α induced apoptosis. Tang et al. and Varfolomeev et al. concluded that sustained JNK activation had resulted from NFκB inhibition [63,64]. Furthermore, it down-regulates the phosphorylated form of NF-κB, p38MAPK, and ERK1/2 protein levels [65]. Based on the literature data, it is evident that in normal cells, PTL protects cells from apoptosis whereas in cancer cells, it supports apoptotic cell death (Table 1).

Parthenolide and ROS

Cellular oxidative stress is defined as enhanced production of intracellular reactive oxygen species (ROS) and/or impaired function of the cellular anti-oxidant defense mechanisms [66]. The intracellular redox status plays an important role in survival and cell death [67]. Most of the cancer therapeutics is apoptosis inducers which disrupt the redox balance by depleting the intracellular thiol buffer system through the removal or redistribution of GSH [68]. The disturbed intracellular redox state elicits the downstream cellular apoptotic events, such as alternation of mitochondrial function and cell signaling pathways, which all lead to cellular death [69]. PTL has also been shown to play a dual role in regulating the intracellular redox state. In HeLa cells, PTL induced cellular apoptosis by enhancing ROS generation which is due to noticeable interactions of PTL with both cytosolic thioredoxin reductase (TrxR1) and mitochondrial thioredoxin reductase (TrxR2) [70]. However, some studies concluded that PTL reacts with the Cys thiols directly and may lead to depletion of intracellular GSH and protein thiols, and induction of ROS in some cancer cells [16,43], and some others suggest that PTL possibly increases GSH levels by activation of the Nrf2-ARE pathway in hippocampal HT22 cells [71]. Interestingly, studies of Li-Weber et al. demonstrated that PTL at low dose (up to 5 μM) neutralizes H_2O_2 generated by the T cell receptor signaling pathway in Jurkat T cells and protects cells from CD3-induced apoptosis, whereas, at high dose (10 μM), it induces $O_2^{\cdot-}$ and generates oxidative stress, leading to an increased number of cell death [72]. Zhang et al. (2004) examined the influence of PTL on mitochondrial function in colorectal cancer cells. PTL activates caspases, dissipates the mitochondrial membrane potential and releases the mitochondrial pro-apoptotic proteins [41]. Therefore, PTL may act as either a pro-oxidant or an antioxidant, under different conditions depending on its concentration and the cell type. It is clear that PTL affects several cellular pathways, modulates cellular redox state and appears to be an efficient drug for anti-cancer therapy (Table 1).

Crosstalk between inflammation and tumorogenesis

Earlier studies from our research group demonstrated that, Biochanin-A, an isoflavone, which is found in red clover, cabbage and alfalfa, is important for the prevention of phosphorylation and degradation of IκBα, thereby blocking NFκB activation and nuclear translocation. This in turn, leads to decreased transcription of the iNOS and other pro-inflammatory genes, thus preventing inflammation. Moreover, Biochanin-A mediated inhibition of inflammatory cytokine release and inhibition of LPS mediated p38 MAPK phosphorylation with its specificity towards cancer cell growth inhibition, indicates the association between antiproliferative and anti-inflammatory actions of Biochanin-A [73]. Parthenolide is also working as an anti-inflammatory and anti-tumorogenic agent in similar manner to that of Biochanin-A. A sesquiterpene lactone 1-β,10-Epoxy-6-hydroxy-1,10H-inunolide (K100) was isolated from *Cota palaestina subsp. syriaca*, an Eastern Mediterranean endemic plant. It was found to be analog of PTL, which inhibited endotoxin induced proinflammatory markers IL-6, MMP-9, and NO in normal mouse mammary SCp2 Cells and showed antiproliferative activity against breast adenocarcinoma MDA-MB-231 cells, indicating its anti-inflammatory and antitumor nature [74]. It indicates that, at least some biologically active components of plants including biochanin, PTL or its analog may work by cross-talking between cellular inflammatory and proliferative pathways. Infection, leading to inflammation has been considered to be major conventional propulsive force of inflammation-induced tumorogenesis. Up to 20% of total cancer cases are allied with microbial infection worldwide [75]. Inflammation and cancer development are associated to each other in the course of processes involving genotoxicity, invasion, metastasis, abnormal tissue repair and also proliferative mechanisms [76]. Numerous experimental records signify that NFκB is involved in the development or progression of human cancers. Several members of NFκB and IκB families were derived from genes that are amplified or translocated in human cancers. The first member of the Rel/NFκB family was *v-rel* oncogene of the reticulo-endotheliosis virus T. In an *in vivo* experiment, REV-T virus was injected in mice which results in aggressive lymphomas [77]. It was reported that NFκB may control apoptosis and cell cycle progression together with invasion and metastasis [78,79]. NFκB constitutively contribute in various tumors, such as breast cancer [80], pancreatic cancer [81], Hodgkin's lymphoma [82] and other. Thus the inhibition of NFκB in cancer cells has become one of the major strategies in anticancer therapy in recent research. Receptor tyrosine kinases are one of most important cell surface growth factor play a crucial role in oncogenesis. Growth factor receptor tyrosine kinases along with ample range of input signals assemble on some major intracellular signaling surges *viz.,* the activation of STAT and this directs to cellular differentiation, adhesion, cell proliferation, transformation, fetal development, inflammation, immune response apoptosis and cell migration [55]. STAT signaling molecule more precisely STAT3, participates in tumorogenesis in multiple tissues, and is strongly linked to inflammatory processes in pancreatic, colon, gastric and lung cancers [83-88]. STAT3 promotes cell proliferation by up-regulating the expression of anti-apoptotic genes *Bcl2* and *Bcl2-like 1* (*Bcl2L1)* [84-85,88], and NFκB [90]. PTL markedly repressed vascular cell migration and capillary-like structure formation and suppressed the expression of angiogenic biomarker proteins VEGF, VEGF receptor 1 and VEGF receptor 2 in both the HUVECs and colorectal cancer cells. Additionally, PTL effectively inhibited tumor neovascularization in a HT-29 xenograft model [91]. In a model of constitutive Wnt activation, elevated NFκB signaling in epithelial cells enhanced Wnt-β-catenin activation and induced dedifferentiation, resulting in intestinal tumorogenesis [92]. Evidently it can be summarized that inflammatory mediators of cellular micro-environment (like cytokines) works individually or cumulatively to promote signals for tumorogenesis (Table 1).

Summary and Conclusion

PTL is the secondary metabolite of feverfew plant (*Tanaceum parthenium*) which has been used in various medical practices worldwide. It can inhibit major cellular inflammatory and proliferation pathways like NFκB, STAT3, MAPK, etc. via blocking them at the transcription level. PTL inhibits the activity and expression of several inflammatory mediators including cyclo-oxygenase (COX). Inflammation represents a physiological response to injury and helps to restore tissue homeostasis. As a result of those cellular immune and inflammatory responses, cell growth, cellular apoptotic signal modulation starts. Acute or prolonged inflammatory processes may lead to increased tissue damage and uncontrolled amplification of inflammatory responses which further proceed towards cancer. Cancer is a multi-factorial class of diseases characterized by uncontrolled cell growth that constitutes the greatest cause of mortality and morbidity worldwide. Inflammation and cancer both are associated with genotoxicity, invasion, metastasis, and abnormal tissue repair mechanisms. In fact, NFκB pathway regulates pro inflammatory cytokine production, leukocyte recruitment and cell survival [93]. In addition, NFκB also controls cell cycle progression and apoptosis together with metastasis and cancer of various types. Elevated NFκB, Wnt/β-catenin pathways are crucial factors of tumorogenesis. PTL inhibits NFκB and Wnt/β-catenin pathways, which exert promising anticancer effects by promoting apoptosis and inhibiting cell proliferation. Furthermore parthenolide altered binding of a number of transcription factors including: C/EBP-α, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT1/3, XBP1 and p53. It depletes GSH and increases cellular oxidative redox status also. *The* disturbed intracellular redox state elicits the downstream cellular apoptotic events, altered mitochondrial function and cell signaling pathways, which all lead to cellular death. Evidently, literature data showed that PTL protects normal cells from apoptosis; whereas it induces apoptosis in cancer cells. PTL has been shown to target acute myelogenous leukemia (AML) stem cells and their progenitors while sparing normal hematopoietic cells [94]. Therefore, parthenolide have become a strong candidate for future anti-cancer therapy in addition to its evident anti-inflammatory nature.

References

1. Hall IH, Lee KH, Starnes CO, Sumida Y, Wu RY, et al. (1979) Anti-inflammatory activity of sesquiterpene lactones and related compounds. J Pharm Sci 68: 537-542.
2. Jain NK, Kulkarni SK (1999) Antinociceptive and anti-inflammatory effects of *Tanacetum parthenium L*. extract in mice and rats. J Ethnopharmacol 68: 251-259.
3. Johnson ES, Kadam NP, Hylands DM, Hylands PJ (1985) Efficacy of feverfew as prophylactic treatment of migraine. Br Med J (Clin Res Ed) 291: 569-573.
4. Biggs MJ, Johnson ES, Persaud NP, Ratcliffe DM (1982) Platelet aggregation in patients using feverfew for migraine. Lancet 2: 776.
5. Mathema VB, Koh YS, Thakuri BC, Sillanpää M (2012) Parthenolide, a sesquiterpene lactone, expresses multiple anti-cancer and anti-inflammatory activities. Inflammation 35: 560-565.
6. Knight DW (1995) Feverfew: chemistry and biological activity. Nat Prod Rep 12: 271-276.
7. Bork PM, Schmitz ML, Kuhnt M, Escher C, Heinrich M (1997) Sesquiterpene lactone containing Mexican Indian medicalplants and pure sesquiterpene lactones as potent inhibitors of transcription factor NF-KappaB. FEBS Lett 402: 85-90.
8. Freeman LW (2009) Mosby's Complementary & Alternative Medicine: A Research-Based Approach. 3rd (Edn) St. Louis, MO: Mosby Elsevier 422-424.
9. Tiuman TS, Ueda-Nakamura T, Garcia Cortez DA, Dias Filho BP, Morgado-Díaz JA, et al. (2005) Antileishmanial activity of parthenolide, a sesquiterpene lactone isolated from *Tanacetum parthenium*. Antimicrob Agents Chemother 49: 176-182.
10. Pareek A, Suthar M, Rathore GS, Bansal V (2011) Feverfew (*Tanacetum parthenium L.*): A systematic review. Pharmacogn Rev 5: 103-110.

11. Sheehan M, Wong HR, Hake PW, Malhotra V, O'Connor M, et al. (2002) Parthenolide, an inhibitor of the nuclear factor-kappaB pathway, ameliorates cardiovascular derangement and outcome in endotoxic shock in rodents. Mol Pharmacol 61: 953-963.

12. López-Franco O, Suzuki Y, Sanjuán G, Blanco J, Hernández-Vargas P, et al. (2002) Nuclear factor-kappa B inhibitors as potential novel anti-inflammatory agents for the treatment of immune glomerulonephritis. Am J Pathol 161: 1497-1505.

13. Hehner SP, Hofmann TG, Dröge W, Schmitz ML (1999) The anti-inflammatory sesquiterpene lactone parthenolide inhibits NF-kappa B by targeting the I kappa B kinase complex. J Immunol 163: 5617-5623.

14. Zhang X, Fan C, Xiao Y, Mao X (2014) Anti-inflammatory and antiosteoclastogenic activities of parthenolide on human periodontal ligament cells in vitro. Evid Based Complement Alternat Med 546097.

15. Gopal YN, Chanchorn E, Van Dyke MW (2009) Parthenolide promotes the ubiquitination of MDM2 and activates p53 cellular functions. Mol Cancer Ther 8: 552-562.

16. Wen J, You KR, Lee SY, Song CH, Kim DG (2002) Oxidative stress-mediated apoptosis. The anticancer effect of the sesquiterpene lactone parthenolide. J Biol Chem 277: 38954-38964.

17. Guzman ML, Rossi RM, Karnischky L, Li X, Peterson DR, et al. (2005) The sesquiterpene lactone parthenolide induces apoptosis of human acute myelogenous leukemia stem and progenitor cells. Blood 105: 4163-4169.

18. Carlisi D, Buttitta G, Di Fiore R, Scerri C, Drago-Ferrante R, et al. (2016) Parthenolide and DMAPT exert cytotoxic effects on breast cancer stem-like cells by inducing oxidative stress, mitochondrial dysfunction and necrosis. Cell Death Dis 7:e2194.

19. Yun BR, Lee MJ, Kim JH, Kim IH, Yu GR, et al. (2010) Enhancement of parthenolide-induced apoptosis by a PKC-alpha inhibition through heme oxygenase-1 blockage in cholangiocarcinoma cells. Exp Mol Med 42: 787-797.

20. Kim JH, Liu L, Lee SO, Kim YT, You KR, et al. (2005) Susceptibility of cholangiocarcinoma cells to parthenolide-induced apoptosis. Cancer Res 65: 6312-6320.

21. Szoltysek K, Pietranek K, Kalinowska-Herok M, Pietrowska M, Kimmel M, et al. (2008) TNFalpha-induced activation of NFkappaB protects against UV-induced apoptosis specifically in p53-proficient cells. Acta Biochim Pol 55: 741-748.

22. Groenewegen WA, Heptinstall S (1990) A comparison of the effects of an extract of feverfew and parthenolide, a component of feverfew, on human platelet activity in-vitro. J Pharm Pharmacol 42: 553-557.

23. Schinella GR, Giner RM, Recio MC, Mordujovich de Buschiazzo P, RÃos JL, et al. (1998) Anti-inflammatory effects of South American *Tanacetum vulgare*. J Pharm Pharmacol 50: 1069-1074.

24. Pugh WJ, Sambo K (1988) Prostaglandin synthetase inhibitors in feverfew. J Pharm Pharmacol 40: 743-745.

25. Uchi H, Arrighi JF, Aubry JP, Furue M, Hauser C (2002) The sesquiterpene lactone parthenolide inhibits LPS- but not TNF-alpha induced maturation of human monocyte-derived dendritic cells by inhibition of the p38 mitogen-activated protein kinase pathway. J Allergy Clin Immunol 110:269-276.

26. Hayes NA, Foreman JC (1987) The activity of compounds extracted from feverfew on histamine release from rat mast cells. J Pharm Pharmacol 39: 466-470.

27. Sumner H, Salan U, Knight DW, Hoult JR (1992) Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components. Biochem Pharmacol 43: 2313-2320.

28. Hwang D, Fischer NH, Jang BC, Tak H, Kim JK, et al. (1996) Inhibition of the expression of inducible cyclooxygenase and proinflammatory cytokines by sesquiterpene lactones in macrophages correlates with the inhibition of MAP kinases. Biochem Biophys Res Commun 226: 810-818.

29. Liao K, Xia B, Zhuang QY, Hou MJ, Zhang YJ, et al. (2015) Parthenolide inhibits cancer stem-like side population of nasopharyngeal carcinoma cells via suppression of the NF-Î°B/COX-2 pathway. Theranostics 5: 302-321.

30. Hehner SP, Heinrich M, Bork PM, Vogt M, Ratter F, et al. (1998) Sesquiterpene lactones specifically inhibit activation of NF-kappa B by preventing the degradation of I kappa B-alpha and I kappa B-beta. J Biol Chem 273: 1288-1297.

31. Kim SL, Liu YC, Seo SY, Kim SH, Kim IH et al. (2015) Parthenolide induces apoptosis in colitis-associated colon cancer, inhibiting NF□B signaling. Oncol Lett 9: 2135-2142.

32. Trubiani O, Salvolini E, Vignini A, D'Arcangelo C, Di Primio R, et al. (2005) NF-kappaB and NOS may play a role in human RPMI-8402 cell apoptosis. Cell Biol Int 29: 529-536.

33. Fan M, Ahmed KM, Coleman MC, Spitz DR, Li JJ (2007) Nuclear factor-kappa B and manganese superoxide dismutase mediate adaptive radioresistance in low-dose irradiated mouse skin epithelial cells. Cancer Res 67:3220-3228.

34. Wang T1, Zhang X, Li JJ (2002) The role of NF-kappaB in the regulation of cell stress responses. Int Immunopharmacol 2: 1509-1520.

35. Saadane A, Masters S, DiDonato J, Li J, Berger M (2007) Parthenolide inhibits IkappaB kinase, NF?Bactivation and inflammatory response in cystic fibrosis cells in mice. Am J Respir Cell Mol Biol 36:728-736.

36. Sobota R, Szwed M, Kasza A, Bugno M, Kordula T (2000) Parthenolide Inhibits Activation of Signal Transducers and Activators of Transcription (STATs) Induced by Cytokines of the IL-6 Family. Biochem Biophys Res Commun 267:329-333.

37. Hwang D, Fischer NH, Jang BC, Tak H, Kim JK, et al. (1996) Inhibition of the expression of inducible cyclooxygenase and proinflammatory cytokines by sesquiterpene lactones in macrophages correlates with the inhibition of MAP kinases. Biochem Biophys Res Commun 226: 810-818.

38. Nam YJ, Lee da H, Lee MS, Lee CS (2015) Sesquiterpene lactone parthenolide attenuates production of inflammatory mediators by suppressing the Toll-like receptor-4-mediated activation of the Akt, mTOR, and NF□B pathways. Naunyn Schmiedebergs Arch Pharmacol 388: 921-930.

39. Fiebich BL, Lieb K, Engels S, Heinrich M (2002) Inhibition of LPS-induced p42/44 MAP kinase activation and iNOS/NO synthesis by parthenolide in rat primary microglial cells. J Neuroimmunol 132: 18-24.

40. Pozarowski P, Halicka DH, Darzynkiewicz Z (2003) Cell cycle effects and caspase-dependent and independent death of HL-60 and Jurkat cells treated with the inhibitor of NF-kappaB parthenolide. Cell Cycle 2: 377-383.

41. Zhang S, Ong CN, Shen HM (2004) Involvement of proapoptotic Bcl-2 family members in parthenolide-induced mitochondrial dysfunction and apoptosis. Cancer Lett 211: 175-188.

42. Nakshatri H, Rice SE, Bhat-Nakshatri P (2004) Antitumor agent parthenolide reverses resistance of breast cancer cells to tumor necrosis factor-related apoptosis-inducing ligand through sustained activation of c-Jun N-terminal kinase. Oncogene 23: 7330-7344.

43. Zhang S, Lin ZN, Yang CF, Shi X, Ong CN, et al. (2004) Suppressed NF-kappaB and sustained JNK activation contribute to the sensitization effect of parthenolide to TNFalpha- induced apoptosis in human cancer cells. Carcinogenesis 25: 2191-2199.

44. Woynarowski JM, Konopa J (1981) Inhibition of DNA biosynthesis in HeLa cells by cytotoxic and antitumor sesquiterpene lactones. Mol Pharmacol 19: 97-102.

45. Hall IH, Williams WL Jr, Grippo AA, Lee KH, Holbrook DJ, et al. (1988) Inhibition of nucleic acid synthesis in P-388 lymphocytic leukemia cells in culture by sesquiterpene lactones. Anticancer Res 8: 33-42.

46. Gopal YN, Arora TS, Van Dyke MW (2007) Parthenolide specifically depletes histone deacetylase 1 protein and induces cell death through ataxia telangiectasia mutated. Chem Biol. 14: 813-823.

47. Fonrose X, Ausseil F, Soleilhac E, Masson V, David B, et al. (2007) Parthenolide inhibits tubulin carboxypeptidase activity. Cancer Res 67: 3371-3378.

48. Kwok BH, Koh B, Ndubuisi MI, Elofsson M, Crews CM (2001) The anti-inflammatory natural product parthenolide from the medicinal herb Feverfew directly binds to and inhibits IkappaB kinase. ChemBiol 8: 759-766.

49. Jeyamohan S, Moorthy RK, Kannan MK, Arockiam AJ (2016) Parthenolide induces apoptosis and autophagy through the suppression of PI3K/Akt signaling pathway in cervical cancer. Biotechnol Lett .

50. Zhang D, Qiu L, Jin X, Guo Z, Guo C (2009) Nuclear factor-kappaB inhibition by parthenolide potentiates the efficacy of Taxol in non-small cell lung cancer in vitro and in vivo. Mol Cancer Res 7: 1139-1149.

51. Kawasaki BT, Hurt EM, Kalathur M, Duhagon MA, Milner JA, et al. (2009) Effects of the sesquiterpene lactone parthenolide on prostate tumor-initiating cells: an integrated molecular profiling approach. Prostate 69: 827-837.

52. Kim SL, Liu YC, Seo SY, Kim SH, Kim IH, et al. (2015) Parthenolide induces apoptosis in colitis-associated colon cancer, inhibiting NF-Î°B signaling. Oncol Lett 9: 2135-2142.

53. Kong FC, Zhang JQ, Zeng C, Chen WL, Ren WX, et al. (2015) Inhibitory effects of parthenolide on the activity of NF-Î°B in multiple myeloma via targeting TRAF6. J Huazhong Univ Sci Technolog Med Sci 35: 343-349.

54. Nakabayashi H, Shimizu K (2012) Involvement of Akt/NF-Î°B pathway in antitumor effects of parthenolide on glioblastoma cells in vitro and in vivo. BMC Cancer 12: 453.

55. Casaletto JB, McClatchey AI (2012) Spatial regulation of receptor tyrosine kinases in development and cancer. Nat Rev Cancer 12: 387-400.

56. Bromberg J (2002) Stat proteins and oncogenesis. J Clin Invest 109: 1139-1142.

57. Kanda N, Seno H, Konda Y, Marusawa H, Kanai M, et al. (2004) STAT3 is constitutively activated and supports cell survival in association with survivin expression in gastric cancer cells. Oncogene 23:4921-4929.

58. Beardmore VA, Ahonen LJ, Gorbsky GJ, Kallio MJ (2004) Survivin dynamics increases at centromeres during G2/M phase transition and is regulated by microtubule-attachment and Aurora B kinase activity. J Cell Sci 117: 4033-4042.

59. Tang TK, Chiu SC, Lin CW, Su MJ, Liao MH (2015) Induction of survivin inhibition, G2/M cell cycle arrest and autophagic on cell death in human malignant glioblastoma cells. Chin J Physiol 58: 95-103.

60. Diamanti P, Cox CV, Moppett JP, Blair A (2013) Parthenolide eliminates leukemia-initiating cell populations and improves survival in xenografts of childhood acute lymphoblastic leukemia. Blood 121:1384-1393.

61. Chang L, Karin M (2001) Mammalian MAP kinase signalling cascades. Nature 410: 37-40.

62. Won YK, Ong CN, Shi X, Shen HM (2004) Chemopreventive activity of parthenolide against UVB-induced skin cancer and its mechanisms. Carcinogenesis 25: 1449-1458.

63. Tang G, Minemoto Y, Dibling B, Purcell NH, Li Z, et al. (2001) Inhibition of JNK activation through NF-kappaB target genes. Nature 414: 313-317.

64. Varfolomeev EE, Ashkenazi A (2004) Tumor necrosis factor: an apoptosis JuNKie? Cell 116: 491-497.

65. Popiolek-Barczyk K, Kolosowska N, Piotrowska A, Makuch W, Rojewska E, et al. (2015) Parthenolide Relieves Pain and Promotes M2 Microglia/Macrophage Polarization in Rat Model of Neuropathy. Neural Plast 2015:676473.

66. Buttke TM, Sandstrom PA (1994) Oxidative stress as a mediator of apoptosis. Immunol Today 15: 7-10.

67. Hampton MB, Orrenius S (1998) Redox regulation of apoptotic cell death. Biofactors 8: 1-5.

68. Duan D, Zhang J, Yao J, Liu Y, Fang J (2016) Targeting Thioredoxin Reductase by Parthenolide Contributes to Inducing Apoptosis of HeLa Cells. J Biol Chem 291: 10021-10031.

69. Herrera F, Martin V, Rodriguez-Blanco J, GarcÃa-Santos G, AntolÃn I, et al. (2005) Intracellular redox state regulation by parthenolide. Biochem Biophys Res Commun 332: 321-325.

70. Ghibelli L, Coppola S, Rotilio G, Lafavia E, Maresca V, et al. (1995) Non-oxidative loss of glutathione in apoptosis via GSH extrusion. Biochem Biophys Res Commun 216: 313-320.

71. Bostwick DG, Alexander EE, Singh R, Shan A, Qian J et al. (2000) Antioxidant enzyme expression and reactive oxygen species damage in prostatic intraepithelial neoplasia and cancer. Cancer 89: 123-134.

72. Li-Weber M, Palfi K, Giaisi M, Krammer PH (2005) Dual role of the anti-inflammatory sesquiterpene lactone: regulation of life and death by parthenolide. Cell Death Differ 12: 408-409.

73. Kole L, Giri B, Manna SK, Pal B, Ghosh S (2011) Biochanin-A, an isoflavon, showed anti-proliferative and anti-inflammatory activities through the inhibition of iNOS expression, p38-MAPK and ATF-2 phosphorylation and blocking NF□B nuclear translocation. Eur J Pharmacol 653: 8-15.

74. Talhouk RS, Nasr B, Fares MB, Ajeeb B, Nahhas R, et al. (2015) Anti-Inflammatory and Cytostatic Activities of a Parthenolide-Like Sesquiterpene Lactone from Cota palaestina subsp. syriaca. Evid Based Complement Alternat Med 2015:474597.

75. Kuper H, Adami HO, Trichopoulos D (2000) Infections as a major preventable cause of human cancer. J Intern Med 248: 171-183.

76. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, et al. (2013) Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 13: 759-771.

77. Gilmore TD, Temin HM (1986) Different localization of the product of the v-rel oncogene in chicken fibroblasts and spleen cells correlates with transformation by REV-T. Cell 44: 791-800.

78. Wieckowski E, Atarashi Y, Stanson J, Sato TA, Whiteside TL (2007) FAP-1-mediated activation of NF-kappaB induces resistance of head and neck cancer to Fas-induced apoptosis. J Cell Biochem 100: 16-28.

79. Montagut C, Tusquest I, Ferrer B, Corominas JM, Bllosillo B, et al. (2006) Activation of nuclear factor kappa B is linked to resistance to neoadjuvant chemotherapy in breast cancer patients. Endocr Relat Cancer 13:607-616.

80. Wu JT, Kral JG (2005) The NF-kappaB/IkappaB signaling system: a molecular target in breast cancer therapy. J Surg Res 123: 158-169.

81. Braeuer SJ, Bunker C, Mohr A, Zwacka RM (2006) Constitutively activated nuclear factor-kappa B, but not induced NF-□B, leads to TRAIL resistance by up-regulation of X-linked inhibitor of apoptosis protein in human cancer cells. Mol Cancer Res 4:715-728.

82. Horie R, Watanabe T (2003) The biological basis of Hodgkin's lymphoma. Drug News Perspect 16: 649-656.

83. Fukuda A, Wang SC, Morris JP 4th, Folias AE, Liou A, et al. (2011) Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. Cancer Cell 19: 441-455.

84. Lesina, M. Kurkowski MU, Ludes K, Rose-John S, Treiber M et al. (2011) Stat3/Socs3 activation by IL 6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell 19: 456-469.

85. Bollrath J, Phesse TJ, von Burstin VA, Putoczki T, BenneckeM, et al. (2009) gp130 mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 15: 91-102.

86. Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, et al. (2009) IL 6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 15: 103-113.

87. Bronte-Tinkew DM, Terebiznik M, Franco A, Ang M, Ahn D, et al. (2009) *Helicobacter pylori* cytotoxin-associated gene A activates the signal transducer and activator of transcription 3 pathway in vitro and in vivo. Cancer Res 69: 632-639.

88. Gao SP, Mark KG, Leslie K, Pao W, Motoi N, et al. (2007) Mutations in the EGFR kinase domain mediate STAT3 activation via IL-6 production in human lung adenocarcinomas. J Clin Invest 117: 3846-3856.

89. Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 9: 798-809.

90. Liang J, Nagahashi M, Kim EY, Harikumar KB, Yamada A, et al. (2013) Sphingosine-1 phosphate links persistent STAT3 activation, chronic intestinal inflammation, and development of colitis-associated cancer. Cancer Cell 23: 107-120.

91. Kim SL, Lee ST, Trang KT, Kim SH, Kim IH et al. (2014) Parthenolide exerts inhibitory effects on angiogenesis through the downregulation of VEGF/VEGFRs in colorectal cancer. Int J Mol Med 33: 1261-1267.

92. Schwitalla S, Fingerle AA, Cammareri P, Nebelsiek T, Göktuna SI, et al. (2013) Intestinal tumorigenesis initiated by dedifferentiation and acquisition of stem-cell-like properties. Cell 152: 25-38.

93. Lawrence T (2009) The nuclear factor NF-kappaB pathway in inflammation. Cold Spring Harb Perspect Biol 1: a001651.

94. Baranello MP, Bauer L, Jordan CT, Benoit DSW (2015) Micelle Delivery of Parthenolide to Acute Myeloid Leukemia Cells. Cellular and Molecular Bioengineering 8: 455-470.

Citation: Dey S, Sarkar M, Giri B (2016) Anti-inflammatory and Anti-tumor Activities of Parthenolide: An Update. J Chem Biol Ther 1: 107. doi: 10.4172/2572-0406.1000107